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(71)出願人　000109543
テルモ株式会社
東京都渋谷区幡ヶ谷２丁目44番１号

(72)発明者　飯塚　貴夫
神奈川県足柄上郡中井町井ノ口1500番地
テルモ株式会社内

(72)発明者　難波　亮一
神奈川県足柄上郡中井町井ノ口1500番地
テルモ株式会社内

(72)発明者　渡辺　英二
神奈川県足柄上郡中井町井ノ口1500番地
テルモ株式会社内

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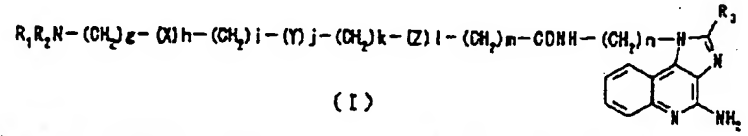
(54)【発明の名称】　インターフェロンを誘起するアミド誘導体を含有する外用剤

(57)【要約】
【課題】アトピー性皮膚炎などの治療剤として有用な、新規なアミド誘導体を含有する外用剤の提供。
【解決手段】下記式Ｉで示されるアミド誘導体及びその医薬的に許容しうる酸付加塩と溶解・吸収促進剤、及び基剤よりなる外用剤。
【化１】



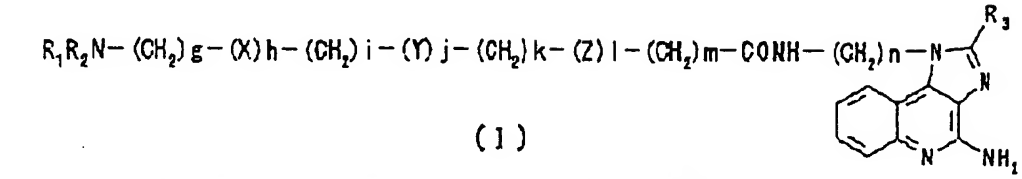
（Ｉ）

（式中、Ｒ1とＲ2は低級アルキル基等、ＸとＹは独立して酸素原子、ＮＲ4、ＣＲ5等（Ｒ4、Ｒ5は独立して水素、芳香環等）、Ｚは芳香環または複素環、Ｒ3は水素、低級アルコキシ基等、ｇ、ｉ、ｋは独立して０～６の整数、ｈ、ｊ、ｌは独立して０または１の整数、ｍは０～５の整数、ｎは２～１２の整数をそれぞれ表す。）

【特許請求の範囲】

【請求項１】下記式Ｉで示されるアミド誘導体及びその医薬的に許容しうる酸付加塩と溶解・吸収促進剤、及び基剤よりなる外用剤。

【化１】



（Ｉ）

（式Ｉ中、R1およびR2は炭素数１から６の分岐していてもよいアルキル基を表し、またR1とR2は一つになって環を形成していてもよい。またR1またはR2のどちらかが、Ｘ、Ｙあるいはメチレン鎖中の任意の原子と一つになって環を形成していてもよい。ＸおよびＹは独立して、酸素原子、Ｓ(Ｏ)ｐ（ｐは０から２の整数を表す。）、ＮR4、ＣR5＝ＣR6、ＣR7R8あるいは置換されていてもよいフェニレン基を表す。ここで、R1、R5、R6、R7およびR8は独立して、水素原子、低級アルキル基、水酸基、低級アルコキシ基、アミノ基、モノあるいはジ低級アルキル置換アミノ基、カルボキシル基、低級アルコキシカルボニル基、置換されていてもよい芳香環基、あるいは置換されていてもよい複素環基を表す。Ｚは芳香環または複素環を表し、低級アルキル基、水酸基、低級アルコキシ基あるいはハロゲンのような置換基を有していてもよい。R3は水素原子、置換されていてもよいフェニル基、低級アルキル基（フェニル基、フェノキシ基、ベンジルオキシ基、低級アルコキシ基、アミノ基、モノあるいはジ低級アルキル置換アミノ基、カルボキシル基、あるいは低級アルコキシカルボニル基で置換されていてもよい。）を表す。ｇ、ｉおよびｋは独立して０から６の整数を表し、ｈ、ｊおよびｌは独立して０または１を表し、ｍは０から５の整数を、ｎは２から１２の整数を表す。）

【請求項２】請求項１に記載のアミド誘導体及びその医薬的に許容しうる酸付加塩の外用剤中における含量が０．００１～１０％（ｗ／ｗ）である請求項１に記載の外用剤。

【請求項３】請求項１に記載のアミド誘導体及びその医薬的に許容しうる酸付加塩を溶解しうる溶解・吸収促進剤がアルコール類（エタノール、エチレングリコール、プロピレングリコール、１，３ブタンジオール、グリセリン等）および／または、高級脂肪酸（イソステアリン酸、オレイン酸等）および／または、本文に定義する有機概念図上において有機性値が３０～１０００、無機性値が５０～１０００、有機性値に対する無機性値の比が０．５～２．０の領域内にある溶解・吸収促進剤から選ばれる少なくとも一種を含有することを特徴とする請求項１または２記載の外用剤。

【請求項４】溶解・吸収促進剤の外用剤中における含量が、０．１～７０％（ｗ／ｗ）である請求項１～３のいずれか１項に記載の外用剤。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は、強力にインターフェロンを誘起し、皮膚好酸球浸潤反応を抑制するアトピー性皮膚炎などの治療剤として有用な新規なアミド誘導体を含有する外用剤である。

【０００２】

【従来の技術】アトピー性皮膚炎の治療には、従来より基本的にステロイド剤の外用と抗ヒスタミン剤あるいは抗アレルギー剤の内服が行われており、その他、減感作療法、アレルゲン（ダニ・食物）除去療法、ＰＵＶＡ（ソラレン-長波長紫外線照射）療法、細菌ワクチン療法などが試みられている。しかし、いずれも決め手となるものではなく、特にステロイド外用剤は、切れ味は良いが長期連投による皮膚の萎縮・毛細血管拡張・潮紅・紫斑・易感染性などの副作用が問題となっている。

【０００３】最近、アトピー性皮膚炎治療の方向はステロイドから作用メカニズムが新規なサイトカイン療法に向かいつつある（中川秀巳，臨床免疫，27[supple 16] 597-602, 1995, 小林祥子ら，臨床免疫，27,[supple 16] 603-609, 1995）。アトピー性皮膚炎患者においては、Ｔｈ１ヘルパー細胞とＴｈ２ヘルパー細胞のバランスの不均衡すなわちＴｈ２細胞優位の状態にあり、Ｔｈ２細胞からのインターロイキン-４やインターロイキン-５などのサイトカインの産生増大の結果、IgE産生や好酸球等の炎症細胞の分化・増殖・浸潤を増強し炎症が惹起されるという説が有力となっている。一般に、感作されたヒトの皮膚に抗原を投与すると投与直後と4～8時間後に最大となり24～48時間持続する皮膚反応が生じる。前者を即時型反応(IgE-肥満細胞が関与)、後者を遅発型アレルギー反応と呼ぶ。特に遅発型反応は喘息を含むアレルギー疾患の病態と密接な関係があると指摘されている。遅発型反応のメカニズムは永らく不明であったが、今日ではIgE-肥満細胞が関与するＩ型アレルギー反応における時間的に遅れた相、すなわちlate phase reactionof the type Ｉ allergy であり、Ｔｈ２ヘルパー細胞優位による好酸球浸潤が深く関わっていると考えられるようになった（黒沢元博，臨床免疫，27(5)，561-574, 1995）。Ｔｈ１ヘルパー細胞とＴｈ２ヘルパー細胞のバランスはインターフェロンによって調節されており、インターフェロ

ン（α、γ）はＴｈ０細胞のＴｈ１細胞への分化を促進する。従って、Ｔｈ２細胞優位を是正するインターフェロン（α、γ）がアトピー性皮膚炎の治療に試みられるようになってきた。

【０００４】インターフェロン療法の主流はリコンビナントなインターフェロンα（Paukkonen K. et. al. :Acta. Derm. Venereol. 73, 141-142, 1993）やインターフェロンγ（Hanifin J. M. :J. Am. Dermatol. 28, 189-197, 1993, Nishioka K. et. al. :J. Dermatol. 22(3), 181-185, 1995）の皮下注射であり、皮膚症状の改善と血中好酸球数の減少が報告されている。インターフェロンは免疫強化作用を有するのでステロイドでよく認められる易感染性等の副作用は認められない。しかし、高コストであることと別の副作用（発熱、感冒様症状、頭痛）が発現するという点でまだ満足できる薬物とは言えない。

【０００５】インターフェロンそれ自身はまだ幾つかの問題を残しているが、低分子化合物のインターフェロン誘起剤が開発されればその局所適用（外用）によってステロイド外用剤及びインターフェロン注射剤の抱えている問題（コストと副作用）を解決できる可能性は高い。これまでインターフェロンを誘起する化合物が幾つか公知となっている。例えば、１-置換-１Ｈ-イミダゾ［４，５-ｃ］キノリン-４-アミン類としては、抗ウイルス剤である１-イソブチル-１Ｈ-イミダゾ［４，５-ｃ］キノリン-４-アミン（ノミキモド）を始めとして幾つか知られている（欧州特許第１４５３４０７、米国特許第４６８９３３８号、米国特許第４６９８３４８号、米国特許第４９２９６２４号、欧州特許第３８５６３０号、米国特許第５３４６９０５号等）。

【０００６】それらのヒトでのインターフェロン誘起活性は低く、また好酸球浸潤抑制作用も記載されていない。したがって、高いインターフェロン誘起活性を持つ化合物を含有し、皮膚局所において好酸球の浸潤を抑制する外用製剤が望まれる。

【０００７】

【発明が解決しようとする課題】従って本発明は、強力なインターフェロン誘起活性による好酸球浸潤抑制作用と優れた経皮吸収性を有し、従ってアトピー性皮膚炎などに有効な新規な化合物を含有する外用剤を提供することにある。

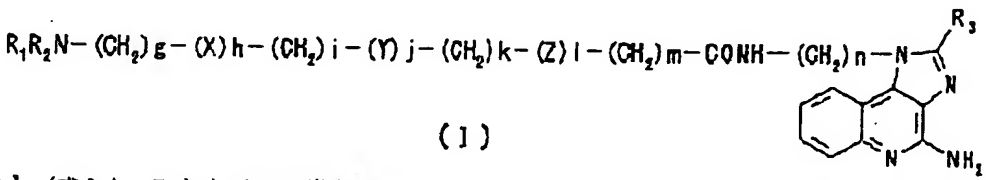
【０００８】

【課題を解決するための手段】上記の課題を解決する本発明は以下の通りである。

【０００９】本発明の外用剤に含まれる化合物は下記式Ｉで示されるアミド誘導体及びその医薬的に許容しうる酸付加塩であり、これらを少なくとも効果を発揮するために十分な量の溶解・吸収促進剤を含有する外用剤を提供する。

【００１０】

【化２】



（Ｉ）

【００１１】（式Ｉ中、R1およびR2は炭素数１から６の分岐していてもよいアルキル基を表し、またR1とR2は一つになって環を形成していてもよい。またR1またはR2のどちらかが、Ｘ、Ｙあるいはメチレン鎖中の任意の原子と一つになって環を形成していてもよい。

【００１２】ＸおよびＹは独立して、酸素原子、Ｓ(O)ｐ（ｐは０から２の整数を表す。）、NR4、CR5=CR6、CR7R8あるいは置換されていてもよいフェニレン基を表す。ここで、R4、R5、R6、R7およびR8は独立して、水素原子、低級アルキル基、水酸基、低級アルコキシ基、アミノ基、モノあるいはジ低級アルキル置換アミノ基、カルボキシル基、低級アルコキシカルボニル基、置換されていてもよい芳香環基、あるいは置換されていてもよい複素環基を表す。

【００１３】Ｚは芳香環または複素環を表し、低級アルキル基、水酸基、低級アルコキシ基あるいはハロゲンのような置換基を有していてもよい。

【００１４】R3は水素原子、置換されていてもよいフェニル基、低級アルキル基（フェニル基、フェノキシ基、ベンジルオキシ基、低級アルコキシ基、アミノ基、モノあるいはジ低級アルキル置換アミノ基、カルボキシル基、あるいは低級アルコキシカルボニル基で置換されていてもよい。）を表す。

【００１５】ｇ、ｉおよびｋは独立して０から６の整数を表し、ｈ、ｊおよびｌは独立して０または１を表し、ｍは０から５の整数を、ｎは２から１２の整数を表す。）

式Ｉで示されるアミド誘導体に医薬的に許容しうる酸付加塩としては、塩酸、臭化水素酸、硫酸、硝酸、リン酸、酢酸、乳酸、マレイン酸、フマル酸、クエン酸、リンゴ酸、酒石酸、シュウ酸、メタンスルホン酸、ｐ-トルエンスルホン酸などの塩が挙げられ、常法により調製される。

【００１６】式Ｉで示されるアミド誘導体の多くは、分子内に不斉炭素を有しラセミ混合物であるが、必要に応じて光学分割、不斉合成などの方法によって各光学活性体を単離し、利用することが可能である。

【００１７】

【発明の実施の形態】本発明の式Ｉで示されるアミド誘導体及びその医薬的に許容される酸付加塩（以下、酸付加塩と略す）は、アトピー性皮膚炎治療剤として投与することができる。

【００１８】外用剤の剤形は、軟膏、クリーム、ローション、ゲル剤、貼付剤、スプレーなどが挙げられる。いずれの剤形においても、調製の際に適当な医薬・製剤的に許容しうる添加物を用いることができる。添加物としては、賦形剤、結合剤、滑沢剤、崩壊剤、希釈剤、風味剤、着色剤、溶解剤、懸濁剤、乳化剤、保存剤、緩衝剤、等張化剤、軟膏基剤、オイル、溶解補助剤、吸収促進剤、接着剤、噴霧剤などが挙げられる。

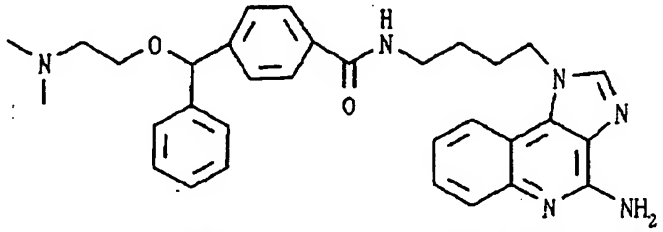
【００１９】式Ｉで示されるアミド誘導体及びその酸付加塩は、好酸球浸潤抑制作用を示すことから、それらの作用が効果を及ぼす他の疾患、たとえばアレルギー性鼻炎、じん麻疹、類天疱瘡、好酸球性膿疱性毛包炎、喘息などに有用であることが示唆される。また、インターフェロンα、γを強力に誘起することから、多発性骨髄腫、腎癌、皮膚悪性腫瘍、膀胱癌、ヘアリー細胞白血病、慢性骨髄性白血病などの各種癌疾患と慢性関節リウマチにも有用である。さらに、Ｂ型、Ｃ型慢性活動性肝炎、単純ヘルペス性角膜炎、性器疣、尖圭コンジローマ、帯状疱疹、ＡＩＤＳなどの各種ウイルス性疾患にも適応可能である。

【００２０】式Ｉに属する最も好ましい化合物は次式で表される。

【００２１】N-[4-(4-Amino-1H-imidazo[4,5-c]quinolin-1-yl)butyl]-4-{[2-(dimethylamino)ethoxy]phenylmethyl}benzamide

【００２２】

【化３】



（Ⅱ）

【００２３】以下、化合物（II）と略す。

【００２４】この化合物は、例えば、以下の方法により合成される。

【００２５】α-（2-ジメチルアミノエトキシ）-α-フェニル-P-トルイル酸０．４４ｇ（１．４７mmol）をクロロホルム１０mlに懸濁し、塩化チオニル０．２１ml（２．９４mmol）を加え、２．５時間加熱還流する。反応液を減圧下濃縮し、酸クロライド体の粗生成物を合成した後、１-（４-アミノブチル）-１H-イミダゾ［４，５-ｃ］キノリン-４-アミン０．３８ｇ（１．４７mmol）をエタノール２２mlと水１５mlの混合溶媒に溶解し、１N-水酸化ナトリウム水溶液１．４７mlを加えた後、氷冷下で先に得られた酸クロライド体のクロロホルム５ml懸濁溶液を加え、２０分間撹拌させる。反応液を炭酸水素ナトリウム水溶液に注ぎ、クロロホルムさらにクロロホルム-メタノール（１０：１(v/v)）混液で抽出し、有機層を乾燥し、溶媒を留去し、残渣をアルミナカラムクロマトグラフィー（クロロホルム：メタノール＝２００：１～３０：１(v/v)）で精製する。最後にエーテルでトリチュレートして濾取し、化合物（II）０．４４ｇ（０．８２０mmol）を微橙白色粉末（ｍｐ：１１０～１１４℃）として得ることができる。

【００２６】式Ｉで示されるアミド誘導体及びその酸付加塩は、外用剤（軟膏剤、クリーム、ローション、ゲル剤）の基剤中で０．００１～１０%、好ましくは０．０４～１%になるように用いられる。

【００２７】この発明では、式Ｉで示されるアミド誘導体及びその酸付加塩が外用剤とするに際して、予め溶解・吸収促進剤に溶解して用いられる。この発明の溶解・吸収促進剤とは、好ましくは化合物を少なくとも０．０１%以上の濃度に溶解しうるもので、かつ外用剤として製剤化された際に式Ｉで示されるアミド誘導体及びその酸付加塩を皮膚から吸収しうるものを意味する。換言すれば式Ｉで示されるアミド誘導体及びその酸付加塩に溶解能と吸収能を付与しうるものである。

【００２８】なお、溶解能または吸収能の一方のみを有するものも、この発明の溶解・吸収促進剤の範囲に包含されるものである。

【００２９】上記２つの要件を満たす基剤を種々検討した結果、次のものが溶解・吸収促進剤として挙げられる。

【００３０】１．アルコール類（エタノール、１，３ブタンジオール、グリセリン等）

２．高級脂肪酸（イソステアリン酸、オレイン酸等）

３．有機概念図Ⅰにおいて有機性値が３０～１０００、無機性値が５０～１０００、有機性値に対する無機性値の比が０．５～２．０の領域内にある溶解・吸収促進剤で、例えば、炭酸低級アルキレン類（炭酸プロピレン、炭酸エチレン等）：界面活性剤（ソルビタンモノラウレート（ＳＰ-２０）、ソルビタンモノステアレート（ＳＰ-６０）、DMSO等）；モノグリセリド（モノステアリン酸グリセリル（MGS）、モノオレイン酸グリセリル（MGO））：クロタミトン。

【００３１】４．これらの混合物

本明細書において、有機概念図とは、すべての有機化合物の根源をメタン（CH4）とし、ほかの化合物はすべてメタンの誘導体とみなしてその炭素数、置換基、変態部、環などにそれぞれ一定の数値を設定し、そのスコアを加算して有機性値及び無機性値を求め、この値を有機性値をｘ軸、無機性値をｙ軸にとった図上にプロットしていくものである。

【００３２】この有機概念図は藤田穆氏の考案によるものであり、その詳細はKUMAMOTO PHARMACEUTICAL BULLETIN, 第１号、第１～１６項（１９５４年）、化学の領域、第１１巻、第１０号、７１９～７２５項（１９５７年）、フレグランスジャーナル、第３４号、第９７～１１１項（１９７９年）、フレグランスジャーナル、第５０号、第７９～８２項（１９８１年）などに説明されている。

【００３３】従って、各化合物の有機概念図はこれらの文献に記載の手法に従って、容易に求めることができる。

【００３４】化合物（II）に好適に用いられる溶解・吸収促進剤とその有機性値と無機性値を表１に示す。

【００３５】

【表１】

表１　化合物(Ⅱ)に対し高い溶解性を示す溶解・吸収促進剤の有機性値、無機性値及び有機性値に対する無機性値の比

化合物	有機性値	無機性値	無機性値/有機性値
化合物（Ⅱ）	６３０	５９７	０.９５

溶解・吸収促進剤	有機性値	無機性値	無機性値/有機性値
クロタミトン	２５０	１５２	０.６１
炭酸プロピレン	８０	９０	１.１３
MGS	４２０	２６０	０.６２
MGO	４２０	２６２	０.６２
DMSO	８０	１４０	１.７５
SP−２０	３６０	４４５	１.２４
SP−６０	４８０	４４５	０.９３

【００３６】一方、化合物（II）に上述した有機性値および無機性値の範囲外で、一般的に使用される溶解基剤、例えば乳酸セチル、セバシン酸ジエチル、オリーブオイル、ヤシ油（ミグリオール８１２）等を用いると溶解性が著しく悪く、溶解・吸収促進剤として適さない。

【００３７】これらの有機性値と無機性値を表２に示す。

【００３８】

【表２】

表２　化合物（Ⅱ）に対し難溶性を示す溶解基剤の有機性値、無機性値及び有機性値に対する無機性値の比

化合物	有機性値	無機性値	無機性値/有機性値
化合物（Ⅱ）	６３０	５９７	０.９５

溶解・吸収促進剤	有機性値	無機性値	無機性値/有機性値
乳酸セチル	３８０	１６０	０.４２
セバシン酸ジエチル	２８０	１２０	０.４２
オリーブオイル	１１４０	１８６	０.１６
ミグリオール８１２	７８０	１８０	０.２３

【００３９】この発明では、式Ｉで示されるアミド誘導体及びその酸付加塩を含有する溶液（溶解、吸収促進剤中）を、外用剤の基剤を用いて当該分野で公知の手段を用いて製剤化される。基剤としては、油脂性基剤（白色ワセリン、流動パラフィン、サラシミツロウ、ひまし油等）が挙げられる。これは、適宜組み合わせて用いるの

が好ましい。

【0040】この発明の外用剤は、上記基剤に加えて、香料、着色剤、防腐剤、高級アルケン酸のような吸収促進剤など外用剤に使用しうる他の添加物や、他の皮膚疾患に有効な薬剤が含まれてもよい。

【0041】この発明の1つの観点によれば、式Iで示されるアミド誘導体及びその酸付加塩を溶解・吸収促進剤に溶解し、得られる溶液と基剤とを混合し、得られる混合物を撹拌または加熱撹拌し、ついで冷却して外用剤を得ることからなる軟膏剤の製法が提供される。

【0042】この方法で1以上の添加剤と、任意に、式Iで示されるアミド誘導体及びその酸付加塩の溶液に用いたのと同じかまたは異なる溶解・吸収促進剤の追加量とを、基剤と同時に加えてもよい。

【0043】なお、この発明の外用剤においては、式Iで示されるアミド誘導体及びその酸付加塩が一部結晶として存在する場合があるが、この場合もこの発明範囲内に包含される。

【0044】この発明の外用剤は皮膚の患部に1日1～6回塗布して使用する事ができる。

【0045】

【実施例】実施例1

本発明による5%化合物（II）軟膏を以下の成分・方法により調整した。

【0046】化合物（II）5gを、ソルビタンモノラウレート（SP-20）25gに80℃で加熱溶解した（A液）。白色ワセリン70gを80℃で加熱溶解したものにA液を加え10分間撹拌し、次いで室温に冷却しながら混合した。

【0047】実施例2

本発明による1%化合物（II）軟膏を以下の成分・方法により調整した。

【0048】化合物（II）1gを、ソルビタンモノラウレート（SP-20）10gに80℃で加熱溶解する（A液）。白色ワセリン89gを80℃で加熱溶解したものにA液を加え10分間撹拌し、次いで室温に冷却しながら混合した。

【0049】実施例3

本発明による0．2%化合物（II）軟膏を以下の成分・方法により調整した。

【0050】化合物（II）0．2gを、ソルビタンモノラウレート（SP-20）10gに80℃で加熱溶解する（A液）。白色ワセリン89．8gを80℃で加熱溶解したものにA液を加え10分間撹拌し、次いで室温に冷却しながら混合した。

【0051】実施例4

本発明による0．04%化合物（II）軟膏を以下の成分・方法により調整した。

【0052】化合物（II）0．04gを、ソルビタンモノラウレート（SP-20）10gに80℃で加熱溶解する（A液）。白色ワセリン89．96gを80℃で加熱溶解したものにA液を加え10分間撹拌し、次いで室温に冷却しながら混合した。

【0053】実施例5

本発明による0．008%化合物（II）軟膏を以下の成分・方法により調整した。

【0054】化合物（II）0．008gを、ソルビタンモノラウレート（SP-20）10gに80℃で加熱溶解する（A液）。白色ワセリン89．992gを80℃で加熱溶解したものにA液を加え10分間撹拌し、次いで室温に冷却しながら混合した。

【0055】実施例6

本発明による1%化合物（II）軟膏を以下の成分・方法により調整した。

【0056】化合物（II）1gを、ソルビタンモノステアレート（SP-60）10gに80℃で加熱溶解する（A液）。ポリオキシエチレン（10）硬化ひまし油（以下、HCO-10と略す）5g、白色ワセリン84gを80℃で加熱溶解したものにA液を加え10分間撹拌し、次いで室温に冷却しながら混合した。

【0057】実施例8

本発明による1%化合物（II）軟膏を以下の成分・方法により調整した。

【0058】化合物（II）1gを、モノステアリン酸グリセリル（MGS）10gに80℃で加熱溶解する（A液）。HCO-10　5g、白色ワセリン84gを80℃で加熱溶解したものにA液を加え10分間撹拌し、次いで室温に冷却しながら混合した。

【0059】実施例9

本発明による1%化合物（II）軟膏を以下の成分・方法により調整した。

【0060】化合物（II）1gを、モノオレイン酸グリセリル（MGO）10gに80℃で加熱溶解する（A液）。HCO-10　5g、白色ワセリン84gを80℃で加熱溶解したものにA液を加え10分間撹拌し、次いで室温に冷却しながら混合した。

【0061】実施例10

本発明による1%化合物（II）軟膏を以下の成分・方法により調整した。

【0062】化合物（II）1gを、1，3-ブタンジオール5gに70℃で加熱溶解した（A液）。一方、ステアリン酸3g、ステアリルアルコール0．5g、ミツロウ0．5g、グリセリルモノステアレート3g、HCO-10　0．5g、セバシン酸ジエチル0．25g、白色ワセリン86．25gを70℃の加温下で溶解し均一に混合した（B液）。次に、B液を60℃の加温下で撹拌しながらA液を加え10分間撹拌し、室温に冷却しながら混合した。

【0063】実施例11

本発明による1%化合物（II）軟膏を以下の成分・方法

により調整した。

【0064】化合物（II）1gを、80℃で加熱したソルビタンモノラウレート（SP-20）5gとクロタミトン2gの混合溶液で溶解した（A液）。HCO-10　5g、白色ワセリン87gを80℃で加熱溶解したものにA液を加え10分間撹拌し、次いで室温に冷却しながら混合した。

【0065】実施例12

本発明による1%化合物（II）クリームを以下の成分・方法により調整した。

【0066】化合物（II）1gを、80℃で加熱したイソステアリン酸10gで溶解後、80℃下でベンジルアルコール2g、セチルアルコール2．2g、ステアリルアルコール3．1g、Polysorbate60　2．55g、ソルビタンモノステアレート0．45gを添加し撹拌溶解した（A液）。一方、グリセリン2g、メチルパラベン0．2g、プロピルパラベン0．02g、精製水76．48gを80℃の加温下で溶解し均一に混合した（B液）。A液、B液をほぼ同じ温度（75℃）に加温し、A液にB液を加えAce Homogenizer(AM-3)（日本精機製作所）で10分間混合（12000rpm）した。次いで、水冷しながら低回転で15分間混合した。

【0067】実施例13

本発明による1%化合物（II）ローションを以下の成分・方法により調整した。

【0068】化合物（II）1gを、70℃で加熱した1，3-ブタンジオール69gで溶解し、精製水30gを加え撹拌した。

【0069】実施例14

本発明による1%化合物（II）ローションを以下の成分・方法により調整した。

【0070】化合物（II）1gを、70℃で加熱した1，3-ブタンジオール49gで溶解し、精製水50gを加え撹拌した。

【0071】実施例15

本発明による1%化合物（II）ローションを以下の成分・方法により調整した。

【0072】化合物（II）1gを、70℃で加熱したソルビタンモノラウレート（SP-20）10gで溶解し、流動パラフィン89gを加え撹拌した。

【0073】比較例1

本発明による1%化合物（II）軟膏を以下の成分・方法により調整した。

【0074】化合物（II）1gを、ミグリオール812　10gに80℃で加熱し懸濁した（A液）。白色ワセリン89gを80℃で加熱溶解したものにA液を加え10分間撹拌し、次いで室温に冷却しながら混合した。

【0075】次にこの発明の軟膏についての経皮吸収試験及び薬理試験について述べる。

【0076】インターフェロン誘起活性

化合物（II）について、ヒトインターフェロン-α測定キット（大塚製薬）とヒトインターフェロン-γ測定キット（BioSource International）を使用してELISA法でIFN量を定量した結果、高いインターフェロン誘起活性を有することが確認された。

【0077】経皮吸収性

（1）試験方法

動物は4週齢のヘアレスマウス（雄）を日本クレア（株）より購入し1週間の馴化期間の後実験に供した。

【0078】経皮吸収性実験は引間知広らの方法(薬剤学, Vol. 55(2), 122-126, 1995）に準じて行った。

【0079】マウスの背部皮膚を無傷の皮膚（インタクトスキン）状態で切り取り、縦型2セル型膜透過実験装置（VIDREZX）に取り付けた。実施例2、実施例8及び比較例1の方法で調整した軟膏（300mg）をドナーセルの皮膚上に加え、レセプターセルにはペニシリン（50U/ml）とストレプトマイシン（50μg/ml）を含むPBSを満たした。レセプター溶液を一定温度（37℃）に保ち、透過実験を行った。経時的にサンプルロから100μlサンプリングし、HPLCにより薬物を定量した。

【0080】この結果より薬物皮膚透過速度を求めた。

【0081】（2）結果

表3に示すように実施例2及び実施例8の製剤が優れた経皮吸収性を示すことが、確認された。

【0082】

【表3】

表3　薬物皮膚透過性

投与薬物	インタクトスキン 化合物（I）透過速度 （μg/cm2/hr）
実施例2	0．478
実施例8	0．450
比較例1	0．032

【0083】皮膚好酸球浸潤抑制作用

マウス皮膚好酸球浸潤モデルにより本製剤の好酸球浸潤

抑制効果を調べる。

【0084】（1）試験方法

①動物飼育方法

動物は4週齢のBalb/cマウス（雄）を日本クレア（株）より購入し室温23±2℃、湿度50±10%（照明時間(8:00-20:00）の条件下で1週間以上の馴化期間の後に実験に供した。実験はすべて非絶食下で行い、被験物投与後の実験期間中は自由に水及び飼料を摂取させた（実験時の体重：18～32g））。

【0085】②感作及び惹起

タンパク量10mg相当のダニ抽出物-Dp（コスモバイオ）にRO水3．8ml、生理食塩水1．2mlを加えタンパク質量2mg/mlの溶液（原液）を調製した。原液を生理食塩水にてタンパク質量500μg/mlに調製した溶液に百日せき菌液を40分の1容量添加したものを感作溶液とした。感作はマイジェクター（テルモ社製）を用い、マウスの頸部の皮下にこの溶液を200μl投与することによって行った。この感作方法で初回感作を含め7日おきに3回感作を行った。

【0086】惹起は初回感作211日後に、生理食塩水で200μg/mlのタンパク濃度に調製したダニ抗原溶液を背部皮内にマイジェクター（テルモ社製）を用いて50μl投与することによって行った。

【0087】③皮膚回収及び病理標本の観察

惹起48時間後に頸椎脱臼によりマウスを屠殺し背部の皮膚を剥ぎ取り、マーキングした部分を中心に1cm四方に皮膚を切断した。回収した皮膚は10%中性ホルマリン緩衝液（コーニングの15ml遠沈管使用）に入れ1日以上室温で放置して固定した。固定した皮膚は、常法にしたがってパラフィン切片作成後、ルナ染色を施した（切り出しは体軸に対し垂直方向に皮膚サンプルの中央と頭側2mm上方の2ヶ所で行った）。標本の観察は光学顕微鏡（400倍）で、1切片1cm当たりの好酸球数を計測した。

【0088】薬剤（被験化合物）による抑制は以下の式から算出した。

【0089】

【数1】

$$\text{抑制率}(\%) = \frac{\text{基材投与群の好酸球数} - \text{被験化合物投与群の好酸球数}}{\text{基剤投与群の好酸球数}} \times 100$$

【0090】④各被験薬物の調製

実施例3～5の軟膏剤を使用した。また、古草酸ベタメタゾンの外用剤は0．12%ジンデロンV軟膏（シオノギ製薬）をそのまま使用した。

【0091】⑤薬物投与方法

経皮投与（密封包帯法：Occlusive dressing technique (ODT)）

マウスをエーテル麻酔して背部中央を電気バリカンで皮膚を傷つけないように除毛した。背部中央の惹起箇所にあたる部分にあらかじめ油性マジックで印を付けた。薬剤（被験化合物）の塗布は、背部の印をつけた部分を中心に前投与では3cm四方に、惹起後は惹起部分を中心に2cm四方に塗布した。さらに、塗布部を覆うようにポリエチレン製の不透性シートをのせ伸縮性テープ（Johnson & Johnson MEDICAL INC：ニラスコチン）で固定した。対照群は基材のみを塗布した。

【0092】投与量は一匹当たり50mg／dayとし、投与スケジュールは以下に示したように惹起前日より4日間連投した。

【0093】惹起前々日　→　惹起日（惹起直後）→　惹起翌日（計3回）

（2）結果

実施例3～5、0．12%古草酸ベタメタゾン軟膏の各被験薬物のダニ惹起マウス皮膚好酸球浸潤反応に対する抑制効果を表4に示す。実施例3、4の軟膏は好酸球浸潤を古草酸ベタメタゾン軟膏（ステロイド）と同等に抑制した（表4）。

【0094】

【表4】

表4　ダニ惹起マウス皮膚好酸球浸潤反応に対する抑制効果

投与薬物及び投与量	例数	好酸球数(個/cm)	抑制率(%)
非感作動物			
非惹起	3	12.0± 3.0	—
感作動物			
ダニ惹起			
基材軟膏	8	1114.3±155.1	—
実施例3	8	316.9±110.2	71.6
実施例4	8	170.0± 33.2	84.7
実施例5	7	542.7±165.9	51.3
吉草酸ベタメタゾン軟膏	8	128.6± 40.3	88.5

惹起2日後の好酸球数を各群 mean±S.E.で示した。

【0095】

【発明の効果】上述した通り、本発明により新規な外用製剤が得られる。本製剤に含まれるアミド誘導体は強力なインターフェロン（α、γ）誘起作用を有し、皮膚好酸球浸潤抑制効果により特にアトピー性皮膚炎の治療に有用である。

フロントページの続き

(72)発明者　上田　美江子
神奈川県足柄上郡中井町井ノ口1500番地
テルモ株式会社内

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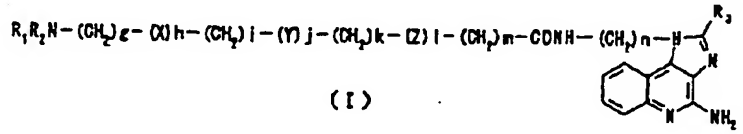
(54) [TITLE OF THE INVENTION]
EXTERNAL DRUG [PREPARATION] THAT INCLUDES AMIDE DERIVATIVE WHICH INDUCES INTERFERON

(57) [ABSTRACT]
[SUBJECTS]
To offer an external drug that includes new amide derivative that is useful as a treatment agent for atopic dermatitis and the like.

[MEASURES OF SOLUTION]
An external drug comprising amide derivative that is shown with chemical formula I below, its acid added salt that can be medicinally tolerated, dissolution and absorption promoter, and a base.

[CHEMICAL FORMULA I]



(I)

(In above formula, R1 and R2 show lower alkyl group and the like; X and Y are each independent and show oxygen atom, NR4, or CR5 and the like (R4 and R5 are each independent, and show hydrogen or aromatic ring and the like); and Z shows aromatic ring or complex ring; and R3 shows hydrogen, or lower alkoxy group and the like; g, i, k are each independent, and show 0 ~ 6 integers; and h,j, and l are each independent and show 0 or 1 integers; and m shows 0~ 5 integers; and n shows 2~ 12 integers.)

(71) Applicant 000109543
Terumo Kabushiki Kaisha [Japanese Company or Corporation]
44-1, 2-chome, Hangatani, Shibuya-ku, Tokyo

(72) Inventor
Takao IIZUKA
c/o Terumo Kabushiki Kaisha
1500-banchi, Inokuchi, Nakai-cho, Ashikagajo -gun, Kanagawa-ken

(72) Inventor
Ryoichi NANBA
same as the above

(72) Inventor
Eiji WATANABE
same as the above

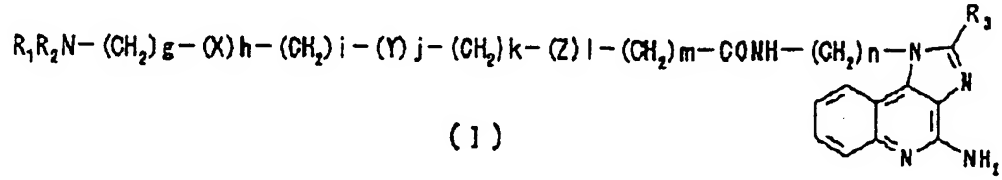
(72) Inventor
Mieko UEDA
same as the above

[Amendments: There are no amendments attached to this patent.]

[note: All names, addresses, company names and brand names are translated in the most common manner. Japanese language does not have singular or plural words unless otherwise specified with numeral prefix or general form of plurality suffix. Translator's note]

[CLAIMS]
[CLAIM ITEM 1]
An external drug comprising amide derivative shown with chemical formula I below, its acid added salt that is medicinally tolerated , dissolution and absorption promoter, and base.

[CHEMICAL FORMULA I]



(1)

(In above formula, R1 and R2 show alkyl group of which carbon 1 through 6 may be branched; and R1 and R2 may become as one to form a ring. In addition, it is all right when either R1 or R2 may become one with X, Y, or optional atom in a methylene chain to form a ring. X and Y are each independent, and shows oxygen atom, $S(O)_p$ (p shows 0 to 2 integers), NR4 CR5=CR6, or phenylene group that may be substituted with CR7R8. At this time, R1, R5, R6, R7 and R8 are each independent, and show hydrogen atom, lower alkyl group, hydroxyl group, lower alkoxy group, amino group, mono or di lower alkyl substituted amino group, carboxyl group, lower alkoxy carbonyl group, or aromatic ring group that may be substituted, or complex ring group that may be substituted. Z shows aromatic ring or complex ring; and it may include substituent such as lower alkyl group, hydroxyl group, lower alkoxy group, or halogen. R3 shows hydrogen atom, phenyl group that may be substituted, lower alkyl group (it may be substituted with phenyl group, phenoxy group, benzyloxy group, lower alkoxy group, amino group, mono or di lower alkyl substituted amino group, carboxyl group, or lower alkoxy carbonyl group). g, i and k are each independent, and show 0 to 6 integers; and h, j and l are each independent, and show 0 to 6 integers; and m shows 0 to 5 integers; and n shows 2 to 12 integers.)

[CLAIM ITEM 2]
The external drug according to the claim item 1, wherein content of amide derivative and its acid added salt that can be medicinally tolerated described in the claim item 1 is 0.001 ~ 10% (w/w).

[CLAIM ITEM 3]
The external drug according to the claim item 1 or 2, wherein dissolution and absorption promoter that can dissolve said amide derivative and its acid added salt that can be medicinally tolerated is of at the least one type selected from alcohols (ethanol, ethylene glycol, propylene glycol, 1,3buttane diol, glycerol and the like) and/or higher fatty acid (isostearic acid, or oleic acid and the like) and/or dissolution and absorption promoter of which organic number being 30 ~ 1000, inorganic number being 50 ~1000 on the organic conceptual diagram defined in this patent, and ratio of inorganic number against organic number being within a range of 0.5 ~ 2.0 .

[CLAIM ITEM 4]
The external drug according to the claim item 1 ~ 3, wherein content of dissolution and absorption promoter within said external drug being 0.1 ~ 70% (w/w).

[DETAILED EXPLANATION OF THE INVENTION]
[0001]
[TECHNICAL FIELDS OF THIS INVENTION]
This invention relates to the external drug that includes new amide derivative that is useful as a treatment agent for atopic dermatitis and the like by inducing interferon forcefully to control skin eosinophile infiltration reaction .

[0002]
[PRIOR ART]

External use of steroids or internal use of anti-histamines or anti-allergic agents have been basically and generally applied for treatments of atopic dermatitis; and besides these methods, desensitization treatment, allergen removal treatment (fleas, foods), PUVA (irradiation of solarene [transliteration]-long wavelength UV rays) or bacterial vaccination treatment method has been attempted for treatment of atopic dermatitis. However, none of these methods have been regarded as the definitive measure; and in particular, despite of its good efficacy, the steroid external preparation presents side-reactions through long term use such as atrophy of skin, expansion of capillary vessels, flush and redness or petechia, or easy infection.

[0003]

The direction of atopic dermatitis treatment is recently moving toward cytokine treatment with new mechanism away from the steroid (make reference to Hidemi NAKAGAWA: Clinical Immunology, 27[supple 16] 597-602, 1995; Shoko KOBAYASHI et al.: Clinical Immunology, 27[supple 16] 603-609, 1995). According to a strong theory applied to the atopic dermatitis patients, inflammation is triggered through IgE production or differentiation, propagation, or infiltration of inflammatory cells such as eosinophile as a result of increase production of cytokine such as interleukin-4 or interleukin-5 of Th2 cells that is caused by an unbalanced state of Th1 herpes cell and Th2 herpes cell, that is to say, a state of dominant Th2 cells. When antigen is administered to an infected human skin, it generally reaches maximum level immediately after such administration and after 4 ~ 8 hours of administration to present skin reaction that prolongs 24 ~ 48 hours. The former case is referred to as an extemporaneous reaction (contributed by IgE-swollen cells) and the latter case is referred to as a delayed-type allergic reaction. In particular, it has been pointed that that the delayed-type reaction to show a close relationship with pathological state of allergic disease that includes asthma. Although mechanism of delayed-type reaction has been unknown for quite some time, current thoughts include time-delayed phase in I-type allergic reaction contributed by IgE-swollen cells, that is to say, a late phase reaction of the type I allergy to indicate a close involvement of eosinophile caused by dominant Th helper cells (make reference to Motohiro KUROSAWA: Clinical Immunology, 27(5), 564-574, 1995). The balance of Th1 helper cells and Th2 helper cells is regulated by interferon; and interferon (α,γ) promotes differentiation of Th0 cells and Th1 cells. And therefore, use of interferon (α,γ) that corrects dominance of Th2 cells has been attempted for the treatment of atopic dermatitis.

[0004]

Regarding the main streams of interferon treatment methods, it includes subcutaneous injection of recombinant interferon α (make reference to Paulkkonen K. et. Al.: Act a, Derm. Venereol. 73, 141-142, 1993) or interferon γ (make reference to Hanifin, J.M.: J. Am. Dermatol. 28, 189-197, 1995, Nishioka K. et. Al.: J. Dermatol. 22(3), 181-185, 1995); and improvement on skin symptoms and reduction of eosinophile in blood have been reported. As interferon shows an immune reinforcement action, side-reactions such as easy inflammation and the like which are often observed in steroid are not recognized. However, it cannot not be regarded as a satisfactory drug from the standpoint of high cost and other side-reactions (fever, flu-like symptoms, headache).

[0005]

Although several issues remain in the interferon itself, when interferon inductive agent of low molecular weight compound is developed for its local application (external use), probability of solving said problems (cost and side-reactions) held by the external drug of steroid and interferon injection drug remains high. Several compounds which induce interferon are already known. For instance, as 1-substitution-1H-imidazo[4,5-c]quinoline4-amines, several agents represented with anti-viral agents such as 1-isobutyl-1H-imidazo[4,5-c]quinoline-4-amine (Imiquimodo [transliteration]) have been known (make reference to European patent 145340, USA patents 4689338; 469834; 4929624; European patent 385630, and USA patent 5346905).

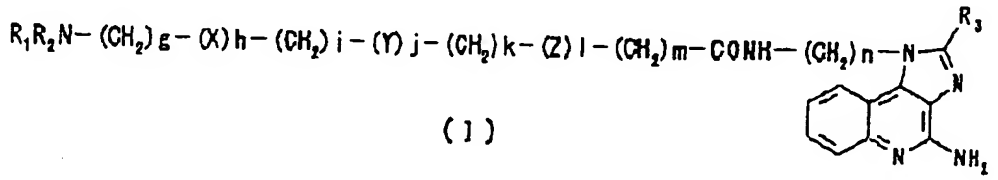
[0006]
The interferon induction activity of these on men remains low, and in addition, eosinophile infiltration controlling action is not described. And therefore, the external drug that includes compound showing high interferon induction activity and controls infiltration of eosinophile at local regions of skin has been desired.

[0007]
[SUBJECTS SOLVED BY THIS INVENTION]
And therefore, this invention offers an external drug that includes new compound that is effective against atopic dermatitis and the like by having eosinophile infiltration controlling action by strong interferon induction activity and shows excellent absorbing action through skin.

[0008]
[MEASURES USED TO SOLVE THE SUBJECTS]
This invention that solves above-explained subjects are further explained below.

[0009]
The compound that is included in this invention's external drug include amide derivative shown with chemical formula I below and its acid added salt that is medicinally tolerated to offer an external drug that includes dissolution and absorption promoter at sufficient quantity at the least to allow display of these effects.

[0010]
[CHEMICAL FORMULA 2]



(1)

[0011]
(In above formula I, R1 and R2 show alkyl group of which 1 through 6 number of carbon atoms may be branched; and R1 and R2 may become one to form a ring. In addition, either R1 or R2 may become one with X, Y, or optional atom within a methylene chain to form a ring.

[0012]
X and Y are each independent, and show oxygen atom $S(O)_p$ (p shows 0 to 2 integer), NR1, CR5=CR6, CR7R8, or phenylene group that can be substituted. At this time, R4, R5, R6, R7, and R8 are each independent, and show hydrogen atom, lower alkyl group, hydroxyl group, lower alkoxy group, amino group, mono or di lower alkyl substituted amino group, carboxyl group, lower alkoxy carbonyl group, aromatic ring group that may be substituted, or complex ring group that may be substituted.

[0013]
Z shows aromatic ring or complex ring; and it may have substituent such as lower alkyl group, hydroxyl group, lower alkoxy group, or halogen.

[0014]
R3 shows hydrogen atom, phenyl group that may be substituted, or lower alkyl group (it may be substituted with phenyl group, phenoxy group, benzyloxy group, lower alkoxy group, amino group, mono or di lower alkyl substituted amino group, carboxyl group, or lower alkoxy carbonyl group).

[0015]

The g, i , and k are each independent , and show 0 to 6 integer; and h,j and l are each independent, and show 0 to 1 integer; and m shows 0 to 5 integer; and n shows 2 to 12 integer.)

As for the acid added salt that can be medicinally tolerated by amide derivative, salts such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, acetic acid, lactic acid, maleic acid, fumaric acid, citric acid, malic acid, tartaric acid, oxalic acid, methane sulfonate, or p-toluene sulfonate and the like may be mentioned; and they may be adjusted by ordinary methods.

[0016]

Many of amide derivatives shown in the chemical formula I have asymmetric carbons within molecules and are racemic mixtures; however, each optical activity may be isolated to be used through optical resolution or asymmetric synthesis and the like.

[0017]

[IMPLEMENTATION FORMAT OFTHIS INVENTION]

The amide derivative shown with chemical formula I and its medicinally tolerable acid added salt (this will be hereafter referred to as acid added salt) of this invention may be administered as a treatment agent against atopic dermatitis.

[0018]

Dosage form of said external drug may include ointment, cream, lotion, gel, patch, or spray and the like. It is possible to use additives which can be tolerated medicinally or drug preparation during adjustment. As said additives, vehicles, binder, lubricant, disintegration, dilutant, flavoring, coloring agents, dissolution agent, suspension agents, emulsifiers, preservatives, buffer agents, isotonicity, ointment base, oil, auxiliary dissolution agent, absorption promoter, adhesive agent, or aerosol and the like may be mentioned.

[0019]

The amide derivative shown in the chemical formula I and its acid added salt show a controlling action against eosinophile infiltration; and therefore, these actions also suggest their efficacy against other diseases, for instance, allergic rhinitis, urticaria, pemphigoid, eosionophilic pustular foliculitis, or asthma. In addition, because it induces interferon α, γ strongly, it is also useful for various cancerous diseases such as multiple myeloma, cancer of kidney, malignant tumor of skin, cancer of bladder, hairy cell leukemia, or chronic bone marrow leukemia and the like, and chronic arthritis as well. In addition, this is applicable against various viral diseases such as B-type, C-type chronic active hepatitis, simple herpes keratitis, vaginal (penal) warts, pointed condyloma or wart, herpes zoster, or AIDS and the like.

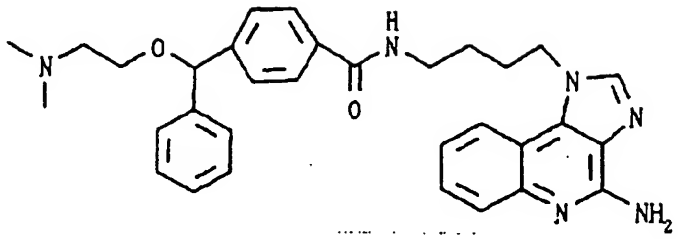
[0020]

The most preferred compound which belong to the chemical formula I may be shown with a formula below.

[0021]

N-[4-(4-Amino-1H-imidazo[4,5-c]quinoline-1-y-butyl]-4-{[2-(dimethylamino) ethoxy] phenyl methyl} benzamide

[0022]
[CHEMICAL FORMULA 3]



(II)

[0023]
This is hereafter abbreviated as compound (II).

[0024]
This compound may be , for instance, synthesized in the manner explained below.

[0025]
0.44g (1.47 mmol) of α-(2-dimethyl amino ethoxy)-α-phenyl-P-toluic acid is suspended in 10 ml of chloroform; and 0.21 ml (2.94 mmol) of thionyl chloride is added, and this is heated and refluxed for 2.5 hours. Reaction solution is condensed under reduced pressure to synthesize crude product of acid chloride; and then, 0.38 g (1.47 mmol) of 1-(4-amino butyl)1H-imidazo[4,5-c]quinoline-4-amine is dissolved in mixed solvent of ethanol 22 ml and water 15 ml; and 1.47 ml of 1N-sodium hydroxide aqueous solution is added, and then, 5 ml of suspended solution of chloroform of acid chloride given by chilling with ice is added, and this is stirred for 20 minutes. Reaction solution is poured into sodium hydrogen carbonate, and this is extracted with chloroform, and furthermore, with a mixture solution with chloroform methanol (10:1 (v/v), and organic layer is dried to hold and remove solvent; and residues are refined with alumina column chromatography (chloroform: methanol = 200:1 ~ 30:1 (v/v)). Lastly, it is filtered and collected through tertulation [transliteration] with ether to give slightly orange and white color powder (mp: 110 ~ 114°C) of the compound (II) 0.44 g(0.820 mmol).

[0026]
The amide derivative shown in the chemical formula I and its acid added salt may be used so it would be 0.001 ~ 10%, or more preferably, 0.04 ~1% within a base of external preparation (ointment, cream, lotion, gel).

[0027]
According to this invention, when external preparation is prepared by using amide derivative shown in the chemical formula I and its acid added salt, it is first dissolved in dissolution and absorption promoter and is used. The dissolution and absorption promoter of this invention dissolve said compound at such concentration of at the least 0.01%; and in addition, it allows absorption of amide derivative shown in the chemical formula I and its acid added salt which are prepared as external drug through skin. In other words, it is capable of providing dissolution capacity as well as absorption capacity to amide derivative shown in the chemical formula I and its acid added salt.

[0028]
Furthermore, scope of this invention's dissolution and absorption promoter includes the ones which may have only either dissolution capacity or absorption capacity as well.

[0029]
After various studies conducted on the base which satisfy above-explained two conditions, following examples may be mentioned as dissolution and absorption promoters:

[0030]

1. ALCOHOLS (ethanol, 1,3-butane diol, or glycerol and the like)
2. HIGHER FATTY ACIDS(isostearate, or oleic acid and the like)
3. DISSOLUTION AND ABSORPTION PROMOTERS SHOWING organic number of 30 ~ 1000, and inorganic number of 50~1000 based on organic conceptual diagram, and ratio of inorganic number based on organic number being within a range of 0.5 ~ 2.0 of which examples include lower alkylene carbonic acid (propylene carbonate, or ethylene carbonate and the like): surfactants (sorbitan monolaurate (SP-20), sorbitan monostearate (SP-60), or DMSO and the like; monoglyceride (glycerol monostearate (MGS)), glycerol mono oleate; and crotamiton .

[0031]

4. mixtures of these.

According to the specification, the term organic conceptual diagram refers to plotting which are taken in following manner: base of all organic compounds is set as methane (CII4), and other compounds are all regarded as derivatives of methane to establish set numeral values on number of carbon atoms, substituent, metamorphosis part, and rings to seek organic number and inorganic number by adding the scores to plot this number on x axis for the organic number and y axis for the inorganic number.

[0032]

This organic conceptual diagram was created by Mr. Kan [transliteration] FUJITA; and its details are explained in KUMAMOTO PHARMACEUTICAL BULLETIN vol. 1, 1 to 16 pages (1954), Domain of Chemistry, vol. 11, No. 10, 719 to 725 pages (1957), Fragrance Journal vol. 34, 97 to 111 page (1979), Fragrance Journal vol. 50, 79 to 82 pages (1981).

[0033]

And therefore, organic conceptual diagram of each compound may be readily sought by using the method described in above-explained references.

[0034]

Dissolution and absorption promoter used in the compound (II) and its organic number and inorganic number are shown in the Table 1.

[0035]

[TABLE 1]

Organic number and inorganic number of dissolution and absorption promoter showing high solubility to the compound (II) and ratio of inorganic number based on organic number

compound	organic number	inorganic number	inorganic number/organic number
compound (II)	630	597	0.95
dissolution & absorption promoters	organic number	inorganic number	inorganic number/organic number
crotamiton	250	152	0.61
propylene carbonate	80	90	1.13
MGS	420	260	0.62
MGO	420	262	0.62
DMSO	80	140	1.75
SP-20	360	445	1.24
SP-60	480	445	0.93

[0036]
On the one hand, when using such dissolution base , for instance, as cetyl lactate, diethyl sebacate, olive oil, or coconut oil (migliol [transliteration] 812) and the like which are used in general of which organic number and inorganic number being out of scope from those explained above on the compound (II), they show a very poor solubility and are not suited as dissolution and absorption promoters.

[0037]
Organic number and inorganic number of these are shown in the Table 2.

[0038]
[TABLE 2] Organic number and inorganic number of dissolution base that shows difficult dissolution against compound (II), and ratio of inorganic number based on organic number

compound	organic number	inorganic number	inorganic number/organic number
compound (II)	630	597	0.95
dissolution & absorption promoters	organic number	inorganic number	inorganic number/organic number
cetyl lactate	380	160	0.42
diethyl sebacate	280	120	0.42
olive oil	1140	186	0.16
migliol 812	780	180	0.23

[0039]
According to this invention, a solution (includes dissolution and absorbing promoter) that includes amide derivative shown with the chemical formula I and its acid added salt is prepared as a drug by using a base for external drug and by already known measures in this field. As for the base, oil and fat base (white Vaseline, liquid paraffin, bleached honey wax, or caster oil and the like) may be mentioned. It is recommended to use these with appropriate combination.

[0040]
The external drug of this invention may include following in addition to above-explained base: other additives which may be used for external preparation such as perfume, coloring agent, absorption promoter such as higher alkenic acid, , or drugs effective against other skin disease.

[0041]
According to one view point of this invention, it offers manufacturing method of ointment by obtaining an external drug by dissolving amide derivative shown with the chemical formula I and its acid added salt in dissolution and absorption promoter, and by mixing thus given solution and base to give a mixture by stirring or heating and stirring, and then, by cooling this to give said external drug .

[0042]
According to this method, it is all right to optionally add either the same or varied quantity of dissolution and absorption promoter used for the solution of more than one types of additives and amide derivative shown with chemical formula I and its acid added salt at the same time as the base.

[0043]
Furthermore, according to this invention's external drug , the amide derivative shown with the chemical formula I and its acid added salt may remain partially as crystals in some cases; and this case is also included in the scope of this invention.

[0044]
The external drug of this invention may be used by coating 1 ~ 6 times /day to the affected region of the skin.

[0045]
[EXAMPLES]
EXAMPLE 1
5% compound (II) ointment by this invention was adjusted by using components and method explained below.

[0046]
5g of compound (II) was heated and dissolved in 25 g of sorbitan monolaurate (SP-20) at 80°C (solution A). Said solution A was added to 70g of white Vaseline that was heated and dissolved at 80°C; and this was stirred for 10 minutes, and then, it was mixed while was cooled to room temperature.

[0047]
EXAMPLE 2
1% compound (II) ointment by this invention was adjusted by using components and method explained below.

[0048]
1 g of compound (II) was heated and dissolved in 10 g of sorbitan monolaurate (SP-20) at 80°C (solution A). Said solution A was added to 89 g of white Vaseline that was heated and dissolved at 80°C; and this was stirred for 10 minutes, and then, it was mixed while was cooled to room temperature.

[0049]
EXAMPLE 3
0.2% compound (II) ointment by this invention was adjusted by using components and method explained below.

[0050]
0.2g of compound (II) was heated and dissolved in 10 g of sorbitan monolaurate (SP-20) at 80°C (solution A). Said solution A was added to 89.8 g of white Vaseline that was heated and dissolved at 80°C; and this was stirred for 10 minutes, and was mixed while was cooled to room temperature.

[0051]
EXAMPLE 4
0.04 % compound (II) ointment by this invention was adjusted by using components and method explained below.

[0052]
0.04 g of compound (II) was heated and dissolved in 10 g of sorbitan monolaurate (SP-20) at 80° (solution A). Said solution A was added to 89.96 g of white Vaseline that was heated and dissolved at 80°C; and this was stirred for 10 minutes, and then, it was mixed while was cooled to room temperature.

[0053]
EXAMPLE 5

0.008 % compound (II) ointment by this invention was adjusted by using components and method explained below.

[0054]

0.008 g of the compound (II) was heated and dissolved in 10 g of sorbitan monolaurate (SP-20) at 80°C (solution A). Then. said solution A was added to 89.992 g of white Vaseline that was heated and dissolved at 80°C; and this was stirred for 10 minutes, and then, it was mixed while was cooled to room temperature.

[0055]
EXCAMPLE 6

1% compound (II) ointment by this invention was adjusted by using components and method explained below.

[0056]

1 g of compound (II) was heated and dissolved in 10 g of sorbitan monostearate (SP-60) at 80°C (solution A). Said solution A was added to 5 g of polyoxy ethylene (10) cured caster oil (this will be hereafter abbreviated as HCO-10) and 84g of white Vaseline which were heated and dissolved at 80°C; and then, this was stirred for 10 minutes, and it was mixed while was cooled to room temperature.

[0057]
EXAMPLE 8

1% compound (II) ointment by this invention was adjusted by using components and method explained below.

[0058]

1g of compound (II) was heated and dissolved in 10 g of glycerol monostearate (MGS) at 80°C (solution A). Said solution A was added to5 g of HCO-10 and 84g of white Vaseline which were heated and dissolved at 80°C; and this was stirred for 10 minutes, and it was mixed while was cooled to room temperature.

[0059]
EXAMPLE 9

1% compound (II) ointment by this invention was adjusted by using components and method explained below.

[0060]

1g of compound (II) was heated and dissolved in 10 g of glycerol monooleate (MG)) at 80°C (solution A). Said solution A was added to 5 g of HCO-10 and 84g of white Vaseline which were heated and dissolved at 80°C, and then, it was stirred for 10 minutes, and was mixed while was cooled to room temperature.

[0061]
EXAMPLE 10

1% compound (II) ointment by this invention was adjusted by using components and method explained below.

[0062]

1 g of compound (II) was heated and dissolved in 5 g of 1,3-butane diol at 70°C (solution A). While on the other hand, 3 g of stearic acid, 0.5 g of stearyl alcohol, 0.5 g of honey bee wax, 3 g of glycerol monostearate, 0.5 g of HCO-10, 0.25 g of diethyl sebacate, and 86.25 g of white Vaseline were dissolved under 70°C heat homogeneously (solution B). Then, while said solution B was stirred under 60°C heating, solution A was added, and was stirred for 10 minutes, and it was mixed while was cooled to room temperature.

[0063]
EXAMPLE 11
1% compound (II) ointment by this invention was adjusted by using components and method explained below.

[0064]
1g of compound (II) was dissolved in mixed solution of 5 g of sorbitan monolaurate (SP-20) and 2 g of crotamiton which were heated at 80°C. Said solution A was added to 87 g of white Vaseline that was heated and dissolved at 80°C; and this was stirred for 10 minutes, and it was mixed while was cooled to room temperature.

[0065]
EXAMPLE 12
1% compound (II) cream by this invention was adjusted by using components and method explained below.

[0066]
1 g of compound (II) was dissolved in 10 g of isostearate that was heated to 80°C; and then, 2 g of benzyl alcohol, 2.2 g of cetyl alcohol, 3.1 g of stearyl alcohol, 2.55 g of polysorbate 60, and 0.45 g of sorbitan monostearate were added at 80°C to dissolve by stirring (solution A). While on the one hand, 2 g of glycerol, 0.2 g of methyl Parabens , 0.02 g of propyl Paragens, and 76.48g of refined water were dissolved and was mixed homogeneously at 80°C (solution B). Solution A and solution B were heated to nearly the same temperature (75°C), and solution B was added to the solution A, and was mixed for 10 minutes in a Acc Homogenizer (AM-3) (made by Nihon Seiki Mfg.) (12000 rpm). Then, it was mixed at low rotation while was cooled with water.

[0067]
EXAMPLE 13
1% compound (II) lotion by this invention was adjusted by using components and method explained below.

[0068]
1 g of compound (II) was dissolved in 69g of 1,3-butane diol heated to 70°C, and 30 g of purified water was added, and was stirred.

[0069]
EXAMPLE 14
1% compound (II) lotion by this invention was adjusted by using components and method explained below.

[0070]
1 g of compound (II) was dissolved in 49 g of 1,3-butane diol heated to 70°C, and 50 g of purified water was added, and was stirred.

[0071]
EXAMPLE 15
1% compound (II) lotion by this invention was adjusted by using components and method explained below.

[0072]
1 g of compound (II) was dissolved in 10 g of sorbitan monolaurate (SP-20) heated to 70°C, and 89g of liquid paraffin was added, and this was stirred.

[0073]
COMPARATIVE EXAMPLE 1

1% compound (II) ointment by this invention was adjusted by using components and method explained below.

[0074]

1 g of compound (II) was heated and suspended in 10 g of migliol at 80°C (solution A). Said solution A was added to 89g of white Vaseline that was heated and dissolved at 80°C; and this was stirred for 10 minutes, and it was mixed while was cooled to room temperature.

[0075]

Skin absorption test and pharmacological tests on the ointments of this invention are explained below.

[0076]
INTERFERON INDUCTION ACTIVITY

Human interferon -α measuring kit (by Otsuka Seiyaku) and human interferon-γ measuring kit (BioSource International) were used on the compound (II) to determine IFN quantity by ELISA method to confirm high interferon induction activity.

[0077]
SKIN ABSORPTION
(1) TEST METHOD

4 weeks old hairless mice (male) were purchased from Nihon Clear K.K. [transliteration] to be used for experiments after 1 week of acclimation period.

[0078]

Transdermal absorption experiment was conducted in accordance with the method by Tomohiro INMA (Pharmacology Vol. 55 (2), 122 - 126, 1955).

[0079]

Back skin of the mice was cut out in an intact skin state, and this was attached to vertical 2 cell type membrane transmission experiment device (VIDREZX). The ointments (300 mg) adjusted in the example 2, example 8, and comparative example 1 were placed on donor cell skin; and receptor cell was filled with PBS that includes penicillin (50L/ml) and streptomycin (50 μg/ml). Receptor solution was held at set temperature (37°C) to conduct transmission experiment. 100 μn sampling was taken from the samples with time to determine drug by HPLC.

[0080]

Skin permeation speed of the drug was sought by the results given above.

[0081]
(2) RESULTS

As shown in the Table 3, drugs of example 2 and example 8 were confirmed to show excellent transdermal absorption.

[0082]
[TABLE 3] Transmission of drugs through skin

administered drug	intact skin, compound (I) permeation speed ($\mu g/cm^2/hr$)
example 2	0.478
example 8	0.450
comparative example 1	0.032

[0083]
CONTROLLING ACTION ON SKIN EOSINOPHILE INFILTRATION

Controlling action of eosinophile infiltration of this drug is studied by using eosinophile infiltration model of mouse skin.

[0084]
(1) TEST METHOD
1. METHOD OF RAISING ANIMALS

4 weeks old Balb/c mice (male) were purchased from Nihon Clear K.K.; and after they were acclimated for at least 1 week under room temperature 23 ±2°C, and humidity 50±10% condition {illumination time (8:00 - 20:00)); and they were subjected to the experiment. Experiments were conducted all under fasting; and during experiments after administration of to-be tested samples, water and feed were provided freely. (weight during experiment: 18 to 32g).

[0085]
2. SENSITIVITY AND TRIGGER

To mite extract -Dp equivalent to 10 mf protein quantity (Cosmobio), 3.8 ml RO water, and 1.2 ml of isotonic sodium chloride solution were added to adjust a solution (original solution) with 2 mg/ml protein mass. The original solution was adjusted with isotonic sodium chloride solution to give 500 μg /ml protein mass; and 1/40 capacity whooping cough bacterium solution was added to give a sensitized solution. Sensitization was conducted by administering this solution 200 μl transdermally at the neck part of mice by using Myjector (made by Terumo Co.). This sensitization was conducted total of 3 times including initial sensitization and every 7 days.

[0086]

Trigger was conducted by administering 50 μl of mite antigen solution that was adjusted to 200μg/ml protein concentration with isotonic sodium chloride solution after 21 days since initial sensitization to the back skin by using Myjector (made by Terumo Co.).

[0087]
3. COLLECTION OF SKIN AND OBSERVATION OF PATHOLOGICAL SAMPLES

After 48 hours of trigger, mouse was destroyed by dislocating cervical part of spinal cord to peel out back skin to cut open 1 cm square centered at marked portion. Thus collected skin was placed in 10% neutral formaline buffer solution (using 15 ml centrifugal tube made by Corning) to leave undisturbed at room temperature for longer than 1 day to fix. Thus fixed skin was prepared as paraffin cut piece by an ordinary manner, and this was subjected lunar [transliteration] dye (cut out was conducted at two location at center of skin sample in perpendicular direction to body axis, and 2 mm above head side). Observation of samples was conducted by using optical microscope (400 x magnification) to calculate eosinophile per 1 cm of one cut piece.

[0088]

Control by drug (testing compound) was calculated with an equation shown below.

[0089]
[formula 1]

$$\text{control rate (\%)} = \frac{\text{number of eosinophile of base administered group - number of eosinophile of to-be tested compound administered group}}{\text{number of eosinophile of base administered group}} \times 100$$

[0090]

4. ADJUSTMENT OF EACH TESTING DRUG

Ointments of examples 3 ~ 5 were used. In addition, as an external preparation of betamethasone valerate , 0.12% of linderone [transliteration] V ointment (made by Shionogi Pharmaceutical) was used as it was.

[0091]

5. ADMINISTRATION METHOD OF DRUGS

Transdermal administration (Occlusive dressing technique (ODT))

Mouse was anesthetized with ether; and center of back part was shaved in such manner so not to damage the skin by using an electric shaver. Marking was applied to the portion equivalent to a trigger portion of the back part by using an oil-base magic marker. Coating of drug (testing compound) was conducted 3 cm square for pre-administration equivalent to the trigger portion that is the center of the back part, and 2 cm square centering trigger portion after trigger. In addition, a polyethylene made non-transparent sheet was placed to cover said coating part and was fixed with a stretch tape (made by Johnson & Johnson MEDICAL INC.: Elascotine [transliteration]). Contrast group was coated only with a base.

[0092]

Administration dosage was set to 50 mg/day per one animal; and administration schedule was set for 1 days from the day prior to trigger as shown below.

[0093]

two days before trigger → trigger date (immediately after trigger)→ next day of trigger (total of 3 times)

(2) RESULTS

Table 4 shows control effects of each testing drug of 0.12 % betamethasone valerate of examples 3 ~ 5 against eosinophile infiltration reaction by mite triggered mouse skin. Ointments of the examples 3 and 4 controlled eosinophile infiltration in the same manner as that of betamethasone valerate ointment (steroid). (refer to Table 4)

[0094]

[TABLE 4] Controlling effect against mite triggered mouse skin eosinophile infiltration reaction

administered drug & administration dosage	example number	number of eosinophile (pieces/cm)	controlling rate (%)
non-sensitized animal non-trigger	3	12.0 ±3.0	-
sensitized animal mite- trigger base ointment	8	1114.3 ± 155.1	-
example 3	8	316.9 ± 110.2	71.6
example 4	8	170.0± 33.2	84.7
example 5	7	542.7± 165.9	51.3
betamethasone valerate ointment	8	128.6± 40.3	88.5

note: numbers of eosinophile after 2 days to trigger are shown with mean ± S.E. of each group.

[0095]

[EFFECTS OF THIS INVENTION]

As explained above, mew external preparation can be obtained by this invention. The amide derivative that is included in this drug shows a strong interferon (α,γ) inducing action; and it is particularly useful for treatment of atopic dermatitis through the controlling effects against skin eosinophile infiltration.

Translation requested by: Auber Staniec, OIPC
Translation by: Mie N. Arntson, 512-331-7167

Therapeutic agent for prevention of arachidonic acid induced dermatological disorders such as psoriasis, mastocytosis and basal cell carcinoma, comprises imiquimod, its salt or solvate as active ingredient

Patent Assignee: JAPAN ENERGY CORP; SUMITOMO SEIYAKU KK

Patent Family

Patent Number	Kind	Date	Application Number	Kind	Date	Week	Type
JP 2000247884	A	20000912	JP 9952523	A	19990301	200064	B

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JP 2000247884	A		4	A61K-031/4745	

Abstract:
JP 2000247884 A

NOVELTY Therapeutic agent for prevention of dermatologic disorders comprises imiquimod, its salt or solvate as active ingredient.

ACTIVITY Antipsoriatic; dermatological; antiinflammatory; cytostatic; anticancer. No test details are given in the specification.

MECHANISM OF ACTION Inhibits arachidonic acid inducing effect. A female mouse (6 weeks old) was pre-breeded for 7 weeks and imiquimod (R837) suspended in acetone at a concentration of 20 mg/ml was applied as a coating at front and back of left auricle. A control was prepared by applying only acetone to the left auricle. Arachidonic acid was applied on the coated auricles and left for 2 hours. The thickness of the right and left auricles were measured. The intracutaneous reaction caused due to antigen inducement was measured. The result showed R837 had an effective inhibitory effect for arachidonic acid induced intracutaneous reaction.

USE For prevention of arachidonic acid induced dermatological disorders such as psoriasis, ultraviolet rays dermatitis, mastocytosis, basal cell carcinoma and barbed cell cancer (claimed).

ADVANTAGE The agent inhibits skin inflammation reaction effectively. The agent inhibits various dermatological disorders associated with arachidonic acid induction.

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